II.B LAPAROSCOPIC SURGICAL APPROACH ARM

II.B Report of Pivotal Clinical Trial Results (G960065) Laparoscopic Use of InFUSE™ Bone Graft/LT-CAGE™ Lumbar Tapered Fusion Device

I. Introduction

Concurrent with the open surgical approach study, FDA granted permission to initiate a laparoscopic surgical approach arm to the IDE. The laparoscopic arm of this IDE (G960065) was conditionally approved by the FDA on September 11, 1998 and full approval was granted in a letter dated December 22, 1998. Except for surgical technique and not having a randomized control treatment, the protocol for the laparoscopic arm was identical to that of the open arm to allow for meaningful data comparisons. A total of 136 patients from 14 investigational sites were enrolled in the study. The first patient had surgery on November 5, 1998 and the last patient had surgery on August 25, 1999. All patients have reached the front end of the 24 month evaluation period window.

This is a report of the clinical findings from the laparoscopic arm of the clinical trial. This report is briefer than the report from the open surgical approach arm since the trial methodology and analytical procedures are identical and do not need repeating.

II. Methods

A. Clinical Trial Goals and Design

The goals of the IDE clinical trial of the InFUSE™ Bone Graft/LT-CAGE™ Lumbar Tapered Fusion Device were to evaluate the safety and effectiveness of the laparoscopic anterior lumbar use of the device in the treatment of patients with symptomatic degenerative disc disease. In this arm of the IDE, the InFUSE™ Bone Graft/LT-CAGE™ device (laparoscopic investigational) was the only treatment. As indicated in the protocol for this arm, the investigational treatment results are to be compared to the control group results from the open surgical approach arm. The laparoscopic InFUSE™ Bone Graft/LT-CAGE™ device data, in particular, surgical parameters as operative time and blood loss, may also be compared to the LT-CAGE™ device (filled with autogenous bone graft) data arising from the IDE clinical trial of the device (G950165). The data from that trial led to PMA approval of the LT-CAGE™ device on September 28, 2000 for both laparoscopic and open surgical approaches.

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The effectiveness of the InFUSE™ Bone Graft/LT-CAGE™ device is based primarily on a patient having radiographically demonstrated fusion, Oswestry pain/disability improvement, and maintenance or improvement in neurological status following surgery. These factors, as well as the patient not having a serious device or device/surgical procedure associated adverse event or having a second surgery classified as a "failure", will determine whether the patient is an overall success – the primary endpoint for the clinical investigation. In addition, back pain, leg pain, disc height status, and general health status will be evaluated. Safety will be based on the nature and frequency of adverse events. The nature and frequency of second surgeries will also be evaluated.

For additional information pertaining to the analyses of the clinical trial results, please refer to the statistical considerations provided in **II.B, Attachment A**.

B. Statistical Methodology

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III. Results

A. Patient Accountability

A summary of the investigational group in this arm of the clinical trial at the various postoperative time periods is provided in **Table 1**. A total of 134 patients received the investigational treatment. In addition, two patients were enrolled into the study but did not receive the study treatment. Please refer to **II.B, Attachment H** for information on these patients. The cut-off date for analyses was July 25, 2001. The postoperative follow-up rates through 24 months exceeded 85%.

B. Surgeon Information

Seventeen (17) surgeons from 14 investigational sites (14 IRBs) participated in the clinical trial. Please refer to **II.B, Attachment B** for a listing of the investigators involved in the clinical trial.

C. Patient Demographics

Demographic information pertaining to the investigational and control treatment groups are presented in **Table 2**. Statistical comparisons were made to determine whether the laparoscopic investigational and open control groups had different patient population characteristics. For the majority of the comparisons, the two treatment groups had very similar demographic characteristics; however, there were a few variables in which statistically significant differences ($p < 0.05$) were noted. These variables included weight, race, alcohol consumption, and preoperative work status. Laparoscopic investigational patients had a lower mean weight than control patients (169.8 lbs. vs. 181.1 lbs.). This difference of approximately 11 lbs. is believed to have little clinical significance and is likely to be a reflection of a higher (not statistically significant) female population in the investigational group as compared to the open control group.

The distribution of races differed between the two treatment groups. The laparoscopic investigational group had more Caucasians than the control group (93.3% vs. 81.6%). This finding is believed to have no clinical relevance.

A higher percentage of the investigational patients admitted to consumption of alcohol preoperatively (49.3% vs. 31.6%). Again this is believed to be of little clinical relevance.

In addition, more investigational patients were working prior to surgery than control patients (52.2% vs. 36.8%). These results may be

indicative of the laparoscopic investigational patients being less disabled prior to surgery, even though this finding can be influenced by a number of factors.

In summary, the laparoscopic investigational and control patients involved in the clinical trial were similar demographically. There were a few parameters in which statistically significant differences were noted, with the work status finding being, perhaps, more important than the others.

D. **Preoperative Medical Condition**

Summaries of the patients' preoperative medical conditions and medications are provided in the **Table 3**. There were several parameters showing statistically significant differences ($p < 0.05$) between the two treatment groups. The laparoscopic investigational group had a lower incidence of previous back surgery (24.6% vs. 40.4%) and a lower usage rate of strong narcotic medication than the control group (12.7% vs. 24.3%). On the other hand, the laparoscopic investigational group was associated with more non-narcotic medication usage (72.4% vs. 55.1%).

Table 4 is a summary of the preoperative radiographic characteristics of degenerative disc disease. These features were considered as part of the patient entry criteria into the study. As evident in the table, the radiographic characteristics of degenerative disc disease for the laparoscopic investigational and control patients were similar. Also, the proportions of patients who had multiple characteristics reported were similar. Since, investigators could mark one or more of the characteristics when enrolling patients, statistical analyses of the proportions are not considered appropriate. The data are being provided for informative purposes.

Table 5 summarizes the preoperative status of the clinical trial endpoints for the treatment groups. The laparoscopic investigational group had statistically significantly higher (better) mean neurological and SF-36 MCS scores, as well as a statistically lower (better) mean leg pain score, than the control group. The mean Oswestry score for the laparoscopic investigational group was lower (better) than the control group mean and the difference approached statistical significance. These findings would tend to indicate that the laparoscopic investigational group had a better preoperative medical condition than the control group. However, the implications of these findings are questionable since subsequent analyses of these parameters involve comparing the postoperative score to the

preoperative score on a patient basis. Such analyses diminish the importance of any baseline differences.

In summary, the preoperative medical conditions of the laparoscopic investigational and control patients involved in the clinical trial tended to be similar. Like the demographic information, statistically significant differences were detected for several of the parameters. The clinical relevance of some of these findings is questionable. However, based on this, one could argue that the laparoscopic investigational patients may have been in a better medical condition prior to surgery. Such was not the case for the open investigational and control groups in which the patients were virtually identical demographically and medically prior to surgery. This is particularly important since the basis for study success and product approval is based primarily on the open approach study. The laparoscopic arm data will be used to support approval for this specific method of implanting the InFUSE™ Bone Graft/LT-CAGE™ device.

E. **Surgery Information**

Table 6 provides summaries of information related to the surgical procedures[1] and postoperative hospitalizations of patients. The results of the statistical analyses between the laparoscopic investigational and control groups are provided in **II.B, Attachment C**. The mean operative times for the two treatment groups were similar with 1.9 hours for the investigational group and 2.0 hours for the control group. The investigational patients were found to have slightly less blood loss than the control group patients (146.1 ml vs. 153.1 ml). The mean hospital stay for the laparoscopic investigational group was statistically lower than the control group (1.2 days vs. 3.3 days). This difference of two days is believed to be clinically relevant as well.

A previous IDE clinical trial was performed on the LT-CAGE™ device (G950165) used with autogenous bone graft. This clinical trial involved the laparoscopic implantation of the cages in single level fusion procedures to treat degenerative disc disease. Of the 266 patients involved in that clinical trial, 223 patients had the

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laparoscopic procedure performed. The surgeries for 37 patients were converted to open procedures intraoperatively due to anatomical issues or vascular injuries. For comparative purposes, the mean operative time, blood loss, and hospital stay for the patients involved in the G950165 trial were 3.1 hrs., 213.6 mls., and 3.0 days, respectively. The values in the current laparoscopic InFUSE™ Bone Graft/LT-CAGE™ device clinical trial are lower in all three categories. This may be attributable to increased surgeon experience with laparoscopic interbody fusion procedures.

A substantial majority of the procedures in both treatment groups involved the L5-S1 level. The laparoscopic investigational group had a higher rate of L5-S1 procedures than in the open control group (84.3% vs. 75.7%).

There was a sizable difference between the two treatment groups in terms of operative approach. The investigational group was dominated by transperitoneal procedures, whereas the control group had more retroperitoneal procedures. This finding is to be expected considering the laparoscopic nature of the investigational surgeries versus the open approach used in the control patients.

Corsets were used more in investigational patients postoperatively than in control patients who tended to be braced. This finding is believed to be associated with surgeon preference and should have no meaningful impact on the results of the study.

More patients in the laparoscopic investigational group were classified as "outpatient/ambulatory" than in the control group. The posterior probability of superiority (for outpatient/ambulatory) for the laparoscopic investigational group was 100.0%. This is a very important finding to patients, hospitals and payers.

In summary, the most meaningful finding was that the laparoscopic investigational patients had shorter hospital stays than control group patients. This is also consistent with the higher proportion of outpatient/ambulatory patients in the laparoscopic investigational group. This is a function of the less invasive nature of the surgical procedure and it is a relevant finding both to the patient as well as the payer. Other differences in surgery and hospital discharge parameters between the treatment groups are believed to be related to the open versus laparoscopic nature of the surgical procedures and should have no material impact on the clinical results.

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F. Safety Measurements

1. Adverse Events

Information pertaining to the adverse events from the laparoscopic investigational treatment group is provided in **II.B, Attachment D**. In addition, **Table 7** provides a time course summary of operative and postoperative adverse events reported for laparoscopic investigational and control patients.[2] In addition, the total number of occurrences and the associated rate of each type of adverse event are provided. The results of statistical analyses of the rates of adverse events between the investigational and control groups are provided in **II.B, Attachment E**.

From Table 7, a total of 92 (68.7%) laparoscopic investigational patients had at least one adverse event. This rate was statistically lower than that for the control group. In addition, adverse events and second surgeries such as nonunions that do not appear on the adverse event table[2] are evaluated for severity and possible cause. Thirteen (9.7%) patients had adverse events or nonunions which were judged to be device associated or device/surgical procedure associated. Many of these events were not considered to be serious. Of those patients having a device associated or device/surgical procedure associated adverse event, only 5 (3.7%) patients had events rated as "serious". These two rates were lower, but not statistically, than those rates for the control group which were 13.2% and 8.8%, respectively.

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2. Radiograhic Reviewer Findings

As part of the review process, the radiographic review teams were asked to indicate if they believed the implant(s) had loosened, bent, broken, or migrated, and if there was evidence of a fractured fusion mass. There were no reports of bent or broken implants nor fractured fusion masses.

There was an occasional observation of implant migration in the laparoscopic investigational group. [redacted] 1 noted implant migration in two patients [redacted] at 6

weeks and in one patient [redacted] at 6 months postoperative.

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The reviewers in Team 2 reported implant migration in only one patient [redacted] at 6 weeks.

There were no findings of implant migration in the control group reported by Teams 1 or 2.

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Review Team 1 noted implant loosening in two laparoscopic investigational patients:

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For comparison in the control group, review Team 1 reported implant loosening in six patients. [redacted]. Review Team 2 reported implant loosening in nine control patients. [redacted]

In addition to the observations pertaining to the implants and fusion mass, members of the radiographic review teams would occasionally write comments on the case report forms. The vast majority of these comments concerned the availability and/or quality of the films. There were 25 laparoscopic investigational patients (18.6%) at 12 months and 20 laparoscopic investigational patients (14.9%) at 24 months for whom overall fusion could not be assessed due to missing or poor quality flexion and extension films or CT scans.

Three patients [redacted] were noted by Team 3 reviewers to have cystic changes or lesions inferior to the implant.

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3. Secondary Surgical Procedures

Some of the adverse events led to surgical interventions subsequent to the clinical trial surgery. These additional surgical interventions can be classified as revisions, removals, supplemental fixations, reoperations, and other. A revision is a procedure that adjusts or in any way modifies the original implant configuration. A removal is a procedure that removes one or more components of the original implant configuration without replacement with the same type of device. A supplemental fixation is a procedure in which additional spinal devices not approved as part of the protocol are placed. A reoperation is any surgical procedure at the involved level that does not remove, modify, or add any original implant components. "Other" surgical procedures are ones that do not fit into the previously mentioned categories and are ones which may not even involve the lumbar spine. **Table 8** provides a summary of the secondary surgical interventions in the laparoscopic investigational and control treatment groups and **II.B, Attachment F** provides the case histories for all second surgery failures in the laparoscopic investigational group. The statistical analyses of the rates of secondary surgical procedures between the laparoscopic investigational group and the control group are provided in **II.B, Attachment G**.

Except for secondary surgical procedures classified as "other", the various rates for the two treatment groups were comparable and there were no statistical differences for any of the comparisons. The laparoscopic investigational group had statistically fewer "other" second surgeries as compared to the control group.

There was one revision procedure in the laparoscopic investigational group. Patient [redacted] had a left neuroforaminal encroachment at L5-S1 and underwent a revision microlumbar decompression with posterior fusion of L5-S1 at 20 months postoperative. No revision procedures occurred in the control treatment group.

There were two implant removal procedures in the laparoscopic investigational group and none in the control group. Both of these removals occurred early in the postoperative phase of the study. One implant removal

occurred in patient [redacted] at one day postoperative as a result of a malpositioned implant. Due to the close proximity to surgery, a histological analyses was not performed on the retrieved implant from this patient.

The other removal occurred in patient [redacted] as a result of issues associated with implant placement and migration. At eight weeks postoperative, this patient underwent a secondary surgery including laparoscopic lysis of adhesions, exploration of L5-S1 fusion site, removal of a displaced right cage, and the placement of posterior instrumentation at the L5-S1 level. [redacted]

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Supplemental fixation procedures occurred at a rate of 5.2% (seven procedures in seven patients) in the laparoscopic investigational group as compared to a 10.3% rate in the control group. The difference in rates approached statistical significance. One laparoscopic investigational patient [redacted] underwent a fusion procedure at the L5-S1 level using pedicle screws in addition to the cage removal referenced above. Two patients [redacted] had supplemental fixation procedures due to the investigators' diagnoses of possible pseudarthroses. One patient [redacted] had one cage removed with a supplemental fixation of the involved level at 1 day postoperative and, later at 7 months postoperative, had an additional reoperation including supplemental fixation of the spinal level below. Another patient [redacted] had a supplemental fixation at eleven months postoperative due to adjacent disc degeneration at the level above. At the time of the supplemental fixation, exploration of the original fusion site confirmed a solid arthrodesis. Another patient [redacted] had a non-union of L5-S1 at 18 months postoperative and underwent a laminectomy and an instrumented posteriolateral fusion of L5-S1. The remaining

patient [redacted] underwent a laminectomy and supplemental fixation at seven months postoperative due to spinal stenosis.

For more information concerning the nature of the reoperation and other second surgery procedures, please refer to **II.A.2, Attachment D.**

In accordance with the protocol, if a study patient had a revision, removal, or supplemental fixation procedure, the patient was then classified as a second surgery "failure". These events were considered in determining overall success for patients. The laparoscopic investigational group had eight second surgery "failures" as compared to fourteen for the control group, both yielding similar rates.

4. Antibody Testing

The report of the antibody test results for the patients involved in the laparoscopic investigational arm of this clinical trial is presented in **II.A.2, Attachment J.** [redacted]

[redacted] **REDACTED** [redacted]

Assay results are available for 129 patients involved in the laparoscopic investigational group.

rhBMP-2 Antibody Results

One laparoscopic investigational patient [redacted] had a 3-month postoperative sample that was positive for antibodies to rhBMP-2 and it was considered an authentic response since the preoperative serum sample was unavailable. To assess the persistence of the antibody response to rhBMP-2, a serum sample was collected at the 12 month postoperative evaluation. This sample tested negative for antibodies to rhBMP-2, and, therefore, the prior positive finding was considered transient. There has been only one adverse event reported for this patient and it was pain in the plantar region of the left foot. In addition, the clinical outcome for this patient was considered an overall success at 12 months. The patient has not been evaluated at 24 months.

The incidence rate of anti-rhBMP-2 antibody formation in the laparoscopic investigational group was 0.8% (1/129), essentially equal to that of the control group, as well as the investigational group in the open surgical approach arm of the clinical trial.

Bovine Type I Collagen Antibody Results

Antibodies to bovine Type I collagen were detected in the postoperative serum samples of 55 laparoscopic investigational patients. Of these, only 32 patients (24.8%) were considered to have authentic elevated antibody responses. This authentic response rate is somewhat higher than the approximate 13% rate noted in both the investigational and control groups in the open arm of the study. One of these laparoscopic investigational patients (100) also had an authentic positive response to rhBMP-2. The remaining 23 laparoscopic investigational patients who had a positive bovine Type I collagen antibody preoperative result did not have a substantial increase in postoperative titer. Five laparoscopic investigational patients had positive preoperative titers but the postoperative samples were unavailable for testing.

The higher rate of authentic positive responses in the laparoscopic investigational group is believed to be due to a higher number of missing preoperative blood samples in this group and the conservative manner taken in assigning authentic positive responses in the presence of missing preoperative samples. If the preoperative sample is missing and the postoperative sample is positive for antibodies, an authentic positive response is declared. There was a total of ten cases in which this happened in the laparoscopic investigational group as compared to only two cases in the control group. If these patients are not considered in the calculations, the rates become very similar (18.5% for the laparoscopic group vs. 11.3% for the control group).

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None of the laparoscopic investigational patients who had a positive response to bovine Type I collagen antibodies tested positive for human Type I collagen.

5. Summary

In summary, the laparoscopic use of the InFUSE™ Bone Graft/LT-CAGE™ device was found to be at least as safe as the control treatment. The adverse event rates were similar with those of the control treatment utilizing the approved LT-CAGE™ device filled with autogenous bone graft.

The rate of graft site related events in the laparoscopic investigational group was found to be statistically better than the rate for the control group. This is considered a very positive result since one of the aspects of using rhBMP-2 is that it precludes the harvesting of bone graft and, in this case, reduces or eliminates a number of related adverse events. The rates of spinal and "Other" adverse events also statistically favored the laparoscopic investigational group as compared to the control group.

There was one category in which there were statistical differences which favored the control group, retrograde

ejaculation. This finding is believed to be related to the laparoscopic surgical technique as opposed to the open procedure used in control patients. The retrograde ejaculation rate in this clinical trial dropped substantially from the rate noted in the previous LT-CAGE™ device trial (10.5% versus 16.2%).

In addition to comparable adverse event rates, the rates of second surgery procedures were similar except for the "other" category which favored the laparoscopic investigational group.

The rate of authentic antibody responses to rhBMP-2 was very low for the laparoscopic investigational group and was very similar to the rates experienced in the control and open investigational groups. The rate of authentic positive responses to bovine collagen antibodies was higher than noted in the control and open investigational groups. The laparoscopic investigational rate is believed to be artificially higher due to missing preoperative blood samples in this group and the conservative manner taken in assigning authentic positive responses in the presence of missing preoperative samples. Patients who had authentic positive responses to bovine collagen antibodies were not found to have positive responses to human Type 1 collagen antibodies. There appeared to be no negative clinical consequence to positive antibody test results.

G. Effectiveness Measurements

The effectiveness variables are identical to those described in the presentation of the open surgical approach arm of the clinical trial. The methods of analyzing the data are also the same and should be referenced for additional information. Therefore, the following section will briefly present the effectiveness results of the laparoscopic arm of the clinical trial. [redacted]

The results of statistical analyses of the effectiveness outcomes, as well as overall success, between the laparoscopic investigational group and the control treatment group are provided in **II.B, Attachment K**.

1. **Fusion**

Table 9 presents the fusion results for the patients in the laparoscopic investigational and control groups. The fusion rates for both treatment groups at 6, 12, and 24 months following surgery were high, greater than or equal to 88%. At 12 months, the fusion rate of the laparoscopic investigational group was 94.1%, as compared to a 92.6% rate for the control group. The laparoscopic investigational group fusion rate at 24 months postoperative was over five percentage points higher than the control group, 94.2% vs. 88.7%. The open investigational group fusion rate at 24 months postoperative was 94.5%.

The Bayesian statistical analyses for comparing 24 month responses showed that the posterior probability of equivalence of the laparoscopic investigational device to the control was 100.0%. The posterior probability of superiority of the investigational device to the control was 89.4%. Based on these probabilities, the fusion rate associated with the laparoscopic use of the investigational device was statistically equivalent to that of the control treatment.

We believe that there was good agreement between the two primary radiographic review teams at [redacted] in terms of assessing fusion. At 12 and 24 months following surgery, the percent agreement between the two teams exceeded 94% for the laparoscopic investigational group. **(II.B, Other Analyses, Appendix A)**.

2. **Pain/Disability**

The mean Oswestry scores for the laparoscopic investigational and control patients at the different clinical trial periods are provided in **Table 10.** At all postoperative time periods for both treatment groups, the mean overall Oswestry scores improved as compared to the preoperative scores. The mean improvement in Oswestry scores favored the laparoscopic investigational group at all postoperative time periods. For example, the Oswestry scores for investigational patients improved from surgery to 24 months by an average of 33.3 points as compared to a 29.5 point value for the control group. The open investigational group patients improved by a mean 29.0 points.

Table 11 shows the distributions of patients demonstrating preoperative to postoperative improvements in Oswestry scores of at least 15 points. Similar to the mean improvement scores, the Oswestry success rates for the laparoscopic investigational group are higher than those of the control group. At 12 months following surgery, the Oswestry success rate for the laparoscopic investigational group was 79.8% as compared to a 75.2% rate for the control group. The 24 month Oswestry success rates for the laparoscopic investigational group was dramatically higher than the control group rate, 87.1% vs. 73.1%. The open investigational group Oswestry success rates at 12 and 24 months were 76.9% and 73.0%, respectively.

Bayesian statistical analyses for comparing 24 month responses showed the posterior probability of equivalence of the laparoscopic investigational device to the control was 100.0% and the posterior probability of superiority of investigational device to the control was 98.8%. Based on these probabilities, the Oswestry success rate associated with the laparoscopic use of the investigational device was statistically superior to that for the control group.

3. **Neurological**

The neurological status of the patients participating in the clinical trial was assessed preoperatively and postoperatively at every follow-up visit. The neurological status assessed motor function, sensory, reflexes, and straight leg raise reproducing pain, as well as overall neurological status. The means of these scores for the treatments groups at the various clinical trial periods are presented in **Table 12**.

Table 13 shows the distributions of patients in the two treatment groups having a maintenance or improvement in conditions following surgery for the various neurological parameters. The overall neurological maintenance or improvement rates at all postoperative time periods for the laparoscopic investigational group were higher than the control group rates.

At 12 months following surgery, the overall neurological success rate for the laparoscopic investigational group was 93.8% as compared to a 84.7% rate for the control group. Similarly at 24 months postoperative, the laparoscopic

investigational group had a higher overall neurological success rate than the control group, 90.2% vs. 83.3%. The overall neurological success rates for the open investigational treatment group were 81.8% and 82.8% at 12 and 24 months, respectively.

Bayesian analyses comparing the 24 month postoperative rates yielded a posterior probability equivalence of 99.9%. The posterior probability of superiority was 93.8%. These results indicate that the overall neurological success rate for the laparoscopic investigational group is equivalent to that for the control group and approached superiority.

4. Back Pain

A summary of back pain scores is provided in **Table 14**. The mean back pain scores at all postoperative time periods were lower than the preoperative mean values for both treatment groups thus indicating significant status improvement following surgery. In addition, the mean improvement scores at 6, 12, and 24 months following surgery were higher for the laparoscopic investigational group as compared to the control group.

Back pain success was determined by comparing the postoperative overall back pain score to the preoperative score on a patient basis. The distributions of patients with successful outcomes are provided in **Table 15**. At 12 months, the laparoscopic investigational group had a back pain success rate of 81.6% and the control group had a success rate of 72.8%. At 24 months following surgery, the laparoscopic investigational group rate was still higher than the control group rate, 84.0% vs. 78.7%. The open investigational group had back pain success rates of 79.1% and 74.6% at 12 and 24 months, respectively.

The Bayesian statistical analyses showed that the posterior probability of equivalence of the laparoscopic investigational device to the control at 24 months was 99.4%. The posterior probability of superiority of investigational device was 81.6%. Based on these probabilities, the back pain results associated with the laparoscopic use of the investigational device is equivalent to that of the control device at 24 months following surgery.

5. **Leg Pain**

Leg pain was assessed in a similar manner to back pain using visual analog scales for pain intensity and duration. A summary of leg pain scores is provided in **Table 16**. The mean leg pain improvement scores for each treatment group were similar and there were significant improvements in condition following surgery.

The distributions of patients with successful leg pain outcomes are provided in **Table 17**. At 12 and 24 months following surgery, the leg pain success rates for the laparoscopic investigational group were higher than those for the control group (81.6% vs. 72.8% and 81.9% vs. 74.1%, respectively). The open investigational leg pain success rate at 12 and 24 months were 72.1% and 80.3%, respectively.

The Bayesian statistical analyses showed that the posterior probability of equivalence of the investigational device to the control at 24 months was 99.6%. The posterior probability of superiority value was 84.1%. Based on these probabilities, the leg pain results associated with the laparoscopic use of the investigational device is equivalent to that of the control device.

6. **General Health**

The Medical Outcomes Study 36-Item Short Form Health Survey (SF-36) was used to assess general health status of all study patients. **Table 18** presents the mean scores of the eight SF-36 scales, as well as the PCS and MCS, at various study periods. Higher scores represent higher levels of health.

In terms of the mean PCS and MCS results, all postoperative scores were higher than preoperative scores for both treatment groups. The mean improvements in PCS and MCS scores from preoperative to 12 months following surgery for the laparoscopic investigational group (14.9 and 6.2 points, respectively) were comparable to the values for the control group (11.1 and 8.1, respectively). At 24 months postoperative, the mean PCS score improvement in the laparoscopic investigational and control treatment groups were 17.0 and 12.2 points, respectively. Mean improvements in MCS scores at 24 months were 5.9 and 7.5 points, respectively.

Tables 19 presents the proportions of patients who demonstrated maintenance or improvement in SF-36 results postoperative as compared to the preoperative condition. With particular focus on the summary parameters, the PCS success rates at 12 and 24 months following surgery for the laparoscopic investigational group were higher than those for the control group (89.4% vs. 80.0% at 12 months and 93.6% and 84.3% at 24 months). The open investigational PCS success rates at 12 and 24 months were 90.8% and 85.1%, respectively.

The Bayesian analyses for comparing 24 month PCS success rates showed that the posterior probability of equivalence was 100% and the posterior probability of superiority was 98.2%. Based on these probabilities, the laparoscopic use of the investigational device is not only as good as the control but also is superior to the control in terms of the PCS results.

The control group had a higher MCS success rate than the investigational group (75.2% vs. 69.9%) at 12 months postoperative. However, at 24 months, the laparoscopic investigational group MCS success rate was slightly higher than the control group rate (72.3% vs. 70.4%). The open investigational group MCS success rates at 12 and 24 months postoperative were 65.4% and 66.9%, respectively. The posterior probability of equivalence of 24 month MCS success rates was 97.6%. Therefore, statistical equivalence between the laparoscopic investigational and control treatment groups was demonstrated.

8. **Disc Height**

The rates of disc height maintenance or improvement at 3, 6, 12 and 24 months following surgery are presented in **Table 20**. The disc height success rates at 24 months following surgery were 94.9% and 96.2% for the laparoscopic investigational and control groups, respectively. The open investigational disc height success rate at 24 months was 94.1%. Bayesian analyses comparing the laparoscopic investigational to the control group demonstrated posterior probability of equivalence of 98.6%. Therefore, the laparoscopic investigational and control treatment groups were found to be statistically equivalent in terms of disc height maintenance following surgery.

H. Overall Success

Overall success was the primary endpoint for the clinical trial. The parameter encompassed important safety and effectiveness aspects of the treatment. **Table 21** provides this information for the two treatment groups at 6, 12, and 24 months following surgery.

At 12 months following surgery, the overall success rate for the laparoscopic investigational group was 69.2% as compared to a 60.8% rate for the control group. The overall success rate at 12 months for the open investigational group was 59.7%. The overall success rate for the laparoscopic investigational group at 24 months postoperative was 68.1% as compared to a 56.3% rate for the control group and a 58.8% rate for the open investigational group.

Bayesian statistical analyses comparing the laparoscopic investigational group to control group rates at 24 months revealed posterior probability of equivalence value of 100.0%. The posterior probability of superiority was found to be 96.6%.

Therefore based on these results, the overall success rate for the laparoscopic investigational group was found to be statistically equivalent to the control group rate but statistically superior as well. This finding meets and exceeds the clinical trial objective.

I. Additional Analyses and Data Presentations

1. Patient Satisfaction

Summaries of the responses to the three patient satisfaction questions are provided in **Table 22.** At 12 months, the rates of laparoscopic investigational patients who responded either "definitely true" or "mostly true" were higher for all three questions than either the control or open investigational groups (79.8% vs. 79.0% vs. 77.8%; 74.3% vs. 69.4% vs. 71.0%; 80.5% vs. 70.9% vs. 77.1%, respectively). The comparative results for the laparoscopic investigational group were even more impressive at 24 months postoperative (84.0% vs. 80.4% vs. 81.2%; 78.5% vs. 76.6% vs. 74.6%; 87.1% vs. 76.7% vs. 82.0%, respectively). Therefore it can be concluded that the laparoscopic investigational patients were at least as satisfied as the control and open investigational patients, if not more so.

2. Global Perceived Effect

The results of the global perceived effect questioning are provided in **Table 23**. At 12 and 24 months following surgery,

72.8% and 79.8%, respectively, of the laparoscopic investigational patients indicated that they had either "completely recovered" or were "much improved". These rates compared favorably with the 69.3% and 70.1% rates for the control group and the 67.9% and 70.5% rates for the open investigational group.

3. **Doctor's Perception of Results**

The findings of the responses from the doctors pertaining to their perceptions of the patients' conditions are provided in **Table 24** for the laparoscopic investigational group. At 24 months following surgery, 88.2% of the doctors responded that the laparoscopic investigational patients were in "excellent" or "good" condition. This rate is comparable to the 85.0% value for the control group and the 87.6% rate for the open investigational group

4. **Work Status**

Table 25 shows the work status of patients at various time points in the clinical study. The laparoscopic investigational patients appeared to have better work status values postoperatively than control patients.

The results of Kaplan-Meier analyses involving the days from surgery to work return and adjusted for differences in preoperative work status revealed that the laparoscopic investigational group patients returned to work significantly quicker than control patients [redacted] The median time to return to work for laparoscopic investigational patients was over 20 days shorter than that for the control patients (42.0 days vs. 64.5 days). Please refer to **II.B, Additional Analyses, Appendix B** for these analyses.

5. **Medication Summaries**

Summaries of the medications taken by the laparoscopic investigational and control patients at the various study periods are provided in **II.B, Additional Analyses, Appendix C**.

6. **Intent to Treat**

An "intent-to treat" analysis was performed and the results are presented in **Table 26**. For this analysis, secondary surgery failures, deaths, patients lost-to-follow-up, and missing observations due to other causes resulted in missing observations for the outcome variables and therefore were

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included in the denominators of the calculated rates, i.e., considered as "failures". By treating these patients as treatment failures, the clinical outcome rates in the intent-to-treat analyses were lower than those observed in the clinical data. Notwithstanding, the 24 month overall success rate for the laparoscopic investigational group was similar to that of the control group (46.3% vs. 49.3%). The lower overall success rate for the laparoscopic investigational group in the "intent-to-treat" presentation as compared to the control group is a reflection of the lower 24 month follow-up rate in the former group. At the time of database closure for analyses, control group follow-up at 24 months was virtually complete, whereas many laparoscopic investigational patients were in their 24 month window..

7. **Examination of Effectiveness Variables by Investigator**
Information pertaining to the effectiveness results at 12 and 24 months by investigator is presented in **II.B, Additional Analyses, Appendix D** for the laparoscopic investigational group.

8. **Financial Disclosure of Clinical Investigators**

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9. Data Listings

Data listings for the laparoscopic investigational patients are provided in **II.B, Attachment M**.

IV. Conclusions

The goal of this treatment arm of the InFUSE™ Bone Graft/LT-CAGE™ Lumbar Tapered Fusion Device IDE clinical trial (G960065) was to evaluate the safety and effectiveness of the laparoscopic anterior spinal use of the device in the treatment of patients with symptomatic degenerative disc disease as compared to a control implant, the LT-CAGE™ device filled with iliac crest-derived autogenous bone. As demonstrated in this report, the clinical results of the use of the InFUSE™ Bone Graft/LT-CAGE™ device were comparable to the control group results.

The laparoscopic investigational and control patients were similar demographically. There were a few parameters in which statistical differences were noted, with the preoperative work status finding being, perhaps, more important than the others. The preoperative medical conditions of the laparoscopic investigational and control patients involved in the clinical trial also tended to be similar. Statistical differences were detected for several of the parameters; however, the clinical relevance of some of these findings is questionable. Nevertheless, the laparoscopic investigational patients may have been in a better medical condition prior to surgery. Such was not the case for the open investigational and control groups in which the patients were virtually identical demographically and medically prior to surgery. This is particularly important since the basis for study success and product approval is based primarily on the open approach study. The laparoscopic arm data will be used to support approval for this specific method of implanting the InFUSE™ Bone Graft/LT-CAGE™ device.

Patients receiving the laparoscopic surgical implantation of the InFUSE™ Bone Graft/LT-CAGE™ device had similar mean operative times and blood loss values as compared to the patients in the control group. Perhaps, the most meaningful surgery/hospital discharge finding was that the laparoscopic investigational patients had statistically shorter hospital stays than control group patients. This is also consistent with the statistically higher proportion of outpatient/ambulatory patients in the laparoscopic investigational group. This is likely a function of the less invasive nature of the surgical procedure and it is a relevant finding both to the patient as well as the payer. Other differences in surgery and hospital discharge parameters between the treatment groups are believed to be related to the open versus laparoscopic nature of the surgical procedures and should have no material impact on the clinical results.

The laparoscopic use of the InFUSE™ Bone Graft/LT-CAGE™ device was found to be at least as safe as the control treatment. The adverse event rates were similar with those of the control treatment.

The rate of graft site related events in the laparoscopic investigational group was found to be statistically better than the rate for the control group. This is considered a very positive result since one of the aspects of using InFUSE™ Bone Graft is that it precludes the harvesting of bone graft from the iliac crest and, in this case, reduces or eliminates a number of related adverse events.

There was one adverse event category in which there was a statistical difference which favored the control group, retrograde ejaculation. This

finding is believed to be related to the laparoscopic surgical technique as opposed to the open procedure used in control patients. The retrograde ejaculation rate in the current clinical trial dropped substantially from the rate noted in the previous LT-CAGE™ device trial which supported approval of the device (10.5% versus 16.2%).

In addition to comparable adverse event rates, the rates of second surgery procedures were similar except for the "other" category which favored the laparoscopic investigational group.

The rate of authentic antibody responses to rhBMP-2 was very low for the laparoscopic investigational group and was very similar to the rates experienced in the control and open investigational groups. The rate of authentic positive antibody responses to bovine collagen was higher than noted in the control and open investigational groups. The laparoscopic investigational rate is believed to be artificially higher due to missing preoperative blood samples in this group and the conservative manner taken in assigning authentic positive responses in the presence of missing preoperative samples. The bovine Type I collagen antibody rates become similar for the laparoscopic investigational and control groups when this convention is not used. Patients who had authentic positive antibody responses to bovine collagen were not found to have positive antibody responses to human Type 1 collagen. There appeared to be no negative clinical consequence to positive antibody test results.

The following table summarizes the effectiveness results at 24 months for the laparoscopic implantation of the InFUSE™ Bone Graft/LT-CAGE™ device.

InFUSE™ Bone Graft/LT-CAGE™ Device (Laparoscopic)	**24 Month Results**	
	Versus Control	
Endpoint	**Equivalence**	**Superiority**
Overall Success	✓	✓
Fusion	✓	
Oswestry Success	✓	✓
Neurological Success	✓	
Back Pain	✓	
Leg Pain	✓	
SF-36 Success PCS MCS	✓ ✓	✓
Disc Height Success	✓	

As readily evident from the above table, the laparoscopic InFUSE™ Bone Graft/LT-CAGE™ device results at 24 months postoperative were statistically equivalent to the control group results for all effectiveness parameters. In addition, the laparoscopic InFUSE™ Bone Graft/LT-CAGE™ device group demonstrated statistical superiority, based on a posterior probability of 95% or greater, to the control group for overall success – the primary study endpoint. In addition, statistical superiority was demonstrated for the endpoints of Oswestry success and SF-36 PCS success.

Another very important finding from this arm of the clinical trial is that laparoscopic investigational patients returned to work more quickly than control group patients. The time to event analyses of the number of days between surgery and returning to work showed a statistical difference in favor of the investigational group.

Therefore, based on these results, it can be concluded that the InFUSE™ Bone Graft/LT-CAGE™ Lumbar Tapered Fusion Device is safe and effective in the laparoscopic surgical treatment of symptomatic degenerative disc disease of the lumbar spine, and that the data and information presented in this PMA application provide a reasonable assurance of the safety and effectiveness of the device.